Digoxin toxicity

Case for retiring its use in elderly patients?

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Digoxin is one of the oldest cardiac medications still in use. Both the current Canadian guidelines for heart failure and atrial fibrillation and the American College of Cardiology Foundation–American Heart Association guideline for the management of heart failure include digoxin as a treatment option.[1-3] However, it does not have the most favourable efficacy and safety profiles.[4,5] Digoxin has a complex pharmacokinetic profile, a narrow therapeutic range, and multiple drug interactions. In 2013, there were 334 referrals to Canadian poison centres related to digoxin toxicity (personal communication with certified specialists in poison information: Ray Li, Deb Kent [BC], Heather Hudson [Ont], Anne Letarte [QC], MaryAnne Carew, and Kim Sheppard [NS]; 2014). Budnitz et al reported that digoxin was the seventh most common cause of adverse drug event–related emergency hospitalizations in older American adults from 2007 to 2009.[6] We present a case that illustrates an inadvertent adverse drug event related to digoxin use in an elderly patient and review the influences on and manifestations of digoxin toxicity.

EDITOR'S KEY POINTS

- Digoxin dosing needs to be personalized based on multiple patient-specific considerations, including age, renal function, body habitus, comorbid conditions, and medications.
- Practitioners should maintain a high level of suspicion for chronic toxicity in patients using digoxin, especially in women, in those with renal impairment, and in older, frail individuals. Symptoms of digoxin toxicity can occur at therapeutic blood concentrations.
- Digoxin-specific antibodies might be considered in some cases of toxicity; if used, serum digoxin levels after treatment are not useful. Patients who receive digoxin antibody fragment should be monitored for changes in serum potassium level, creatinine level, vital signs, heart failure symptoms, and electrocardiography findings.

POINTS DE REPÈRE DU RÉDACTEUR

- La posologie de la digoxine doit être personnalisée en tenant compte de nombreux facteurs relatifs au patient, dont l'âge, la fonction rénale, la morphologie, les comorbidités et la médication.
- Les praticiens doivent toujours maintenir un niveau de suspicion de toxicité chronique chez les patients sous digoxine, particulièrement les femmes, les personnes aux prises avec une atteinte rénale et les patients âgés et frêles. Les symptômes de toxicité à la digoxine peuvent se manifester à des concentrations sanguines thérapeutiques.
- Dans certains cas de toxicité, on peut envisager le recours aux fragments d'anticorps spécifiques de la digoxine; s'ils sont utilisés, les taux sériques de digoxine après le traitement sont inutiles. Les patients qui reçoivent un fragment d'anticorps anti-digoxine doivent être surveillés pour détecter tout changement dans le taux sérique de potassium et de créatinine, les signes vitaux, les symptômes d'insuffisance cardiaque et les constatations à l'électrocardiogramme.

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Case

Emergency medical services responded to a call from the husband of a 69-year-old woman. He was concerned about her increasing confusion, vomiting, and reduced level of consciousness. On emergency medical services' arrival, the patient's vital signs included a blood pressure of 85/60 mm Hg and heart rate of 30 beats/min. The patient's medical history included atrial fibrillation, congestive heart failure, osteoarthritis (affecting hips and knees), hypothyroidism, peptic ulcer disease, and bipolar disorder. Her medications at the time of admission are listed in **Table 1**.

Laboratory investigations revealed a serum digoxin concentration (SDC) of 7.5 nmol/L (therapeutic range 1.0 to 2.6 nmol/L according to Calgary Laboratory Services), a potassium level of 7.3 mmol/L, and a creatinine level of 186 µmol/L. The patient received intravenous fluids, norepinephrine, and digoxin antibody fragments (5 vials). Four hours later the patient's vital signs improved to a blood pressure of 110/80 mm Hg and a heart rate of 58 beats/min. Seventy-two hours later, the patient's vital signs remained stable and her creatinine level was 93 µmol/L. All her medications were restarted, and she was prepared for discharge home.

Discussion

We searched MEDLINE, EMBASE, and the International Pharmaceutical Abstracts using the key words *digoxin* and *toxicity,* limiting the search to studies of oral formulations in adults, published in English.

Table 1. Patient's medications on admission

MEDICATION	DOSAGE
Rivaroxaban	20 mg/d
Diltiazem	240 mg/d
Digoxin	0.25 mg/d
Nitroglycerin patch	0.2 mg/h to be worn 10 h/d
Spironolactone	100 mg (1 tablet in the morning and half a tablet at lunch)
Furosemide	40 mg/d
Celecoxib	200 mg/d
Levothyroxine	100 µg/d
Lansoprazole	30 mg/d
Escitalopram	15 mg/d
Amitriptyline	75 mg at bedtime
Quetiapine	100 mg twice daily
Olanzapine	10 mg at bedtime
Nitrofurantoin	50 mg at bedtime
Zopiclone	5 mg at bedtime as needed

Digoxin dosing, mechanism of action, pharmacokinetics, and monitoring. Oral digoxin is available as a solution (0.05 mg/mL) or as tablets (0.0625 mg, 0.125 mg, and 0.25 mg).[7] Dosing should be initiated and maintained at doses of 0.125 to 0.25 mg daily, with lower doses considered in patients 70 years of age or older.[3] Historically, the upper therapeutic range for SDC was 2.0 nmol/L.[8] However, this upper limit has been adjusted in light of evidence demonstrating that, compared with higher SDCs, patients who were dosed to lower SDCs experienced improved symptom control, fewer hospitalizations, and a decrease in all-cause mortality with fewer safety concerns, particularly in women and frail elderly patients taking doses that achieve an SDC of 1.0 nmol/L or greater.[9-13] The recommended therapeutic SDC is 0.5 to 0.9 nmol/L in patients with congestive heart failure.[3]

Digoxin exerts its positive inotropic effects by reversibly inhibiting the cellular membrane sodium-potassium pump. As a result, there is an increase in intracellular sodium concentration, a reduction in cytoplasmic potassium, and ultimately an increase in cytoplasmic calcium that promotes myocardial contractility.[14] When taken orally, digoxin is incompletely absorbed. Distribution follows a 2-compartment model: the first compartment being plasma and other rapidly equilibrating tissues and the second being more slowly equilibrating tissues—including the myocardium—with a final volume of distribution of 6.3 to 7.3 L/kg.[15,16] Digoxin metabolism occurs via hydrolysis, oxidation, and conjugation in the liver and does not involve the cytochrome P450 system.[17] Up to 70% of an oral dose is cleared unchanged by the kidneys.[15,17] In patients with normal renal function, the half-life of digoxin is about 36 hours; however, this can be prolonged in patients with renal dysfunction.[15]

Manifestations of toxicity. Clinical manifestations of toxicity include gastrointestinal and neurologic symptoms, as well as cardiac dysrhythmia (**Table 2**).[17,18]

Considerations if using digoxin. Assess patient-specific factors that can influence the dose-effect relationship such as age, renal function, body habitus, comorbid conditions, and medications.[10,17-19] Specifically, prescribers should keep in mind the following:

- Functional decline of the liver and especially the kidneys can alter digoxin metabolism and clearance, and is more likely in the elderly.[15,18]
- Digoxin is highly hydrophilic and the dose-effect relationship is dependent on lean body mass; dosage should be based on ideal body weight.[16,20]
- Electrolyte imbalances such as hypomagnesemia, hypercalcemia, hypernatremia, and hypokalemia can alter the effects of digoxin on the myocardium, even when blood concentrations are within the therapeutic range.[21]
- Exacerbations of chronic heart failure can lead to a reduced clearance of digoxin.[19]
- Hypoxia and alkalosis related to chronic pulmonary disease can lead to toxic effects in patients receiving digoxin.[19]

Table 2. Clinical and laboratory manifestations of digoxin toxicity

VARIABLE	ACUTE TOXICITY	CHRONIC TOXICITY
Digoxin concentration	• High	• Therapeutic or moderately elevated
Ocular symptoms	• Not reported	• Possible (yellow or green vision, halos, photophobia)
Neuropsychiatric symptoms	• Altered mental status • Headache • Hallucinations • Convulsions	• Delirium • Drowsiness • Headache • Hallucinations
Gastrointestinal symptoms	• Nausea or vomiting • Abdominal pain • Diarrhea	• Nausea or vomiting • Anorexia or weight loss
Potassium level	• Normal or high	• Low, normal, or high
Cardiac symptoms	• Bradydysrhythmia	• Tachydysrhythmia • Bidirectional ventricular tachycardia

Data from Ehle et al[17] and Hack.[18]

- Thyroid abnormalities alter digoxin kinetics; a hypothyroid state reduces both volume of distribution and clearance while a hyperthyroid state increases both.[16]
- A previous hospital admission for digoxin toxicity is a predictor of subsequent events.[22]

Evaluate a patient's drug profile for any recently started or stopped medications or dosage changes to existing medications. Medication changes can result in pharmacokinetic or pharmacodynamic interactions. Drug interactions might result in rapid increases in digoxin blood concentrations and related toxic symptoms. Commonly reported clinically meaningful drug interactions are listed in **Table 3**.[15-18,22-27] Pharmacodynamic interactions leading to digoxin toxicity might occur without changes in SDC.

Digoxin has a unique interaction with macrolide antibiotics. In 10% to 15% of patients, digoxin is inactivated in the gut by enteric bacteria (primarily *Eubacterium lentum*); inhibition of these bacteria by macrolide antibiotics, in particular clarithromycin, can increase bioavailability.[10,21,23]

Case review. Patient factors potentially influencing digoxin concentrations in this case include hypothyroidism, congestive heart failure, and an acute episode of renal impairment, which might have been exacerbated by the use of celecoxib. Drug interactions with digoxin in this case include celecoxib, furosemide, levothyroxine, and spironolactone. The decision to continue digoxin in this patient is controversial. Two large randomized trials demonstrated worsening heart failure in patients who stopped taking digoxin compared with those who took it to maintain an SDC of 1.2 nmol/L.[28,29] However, neither study included the use of β-blockers, currently considered the criterion standard of care.[2,3] If this patient continues to take digoxin, she is at an increased risk of future episodes of digoxin toxicity and requires close monitoring (both symptomatic and laboratory). Based on the Beers criteria, which strongly recommend against taking more than 0.125 mg daily of digoxin in heart failure, a dose reduction is recommended.[30]

This patient's toxicity management included digoxin antibody fragment. Digoxin antibody fragment use should be considered in the context of life-threatening dysrhythmias, a potassium level greater than 5.0 mmol/L (in acute overdose), an SDC greater than 12 nmol/L, acute adult ingestion of digoxin greater than 10 mg or acute pediatric ingestion of digoxin greater than 4 mg, or undiagnosed or unstable bradycardia. Patients who receive digoxin antibody fragment should be monitored for changes in serum potassium level, creatinine level, vital signs, heart failure symptoms, and electrocardiography findings. Serum digoxin levels will appear to rise immediately following administration of digoxin antibody fragment owing to the presence of inactive Fab-digoxin complex; obtaining a free digoxin concentration (which might not be readily available) is clinically useful.[31]

Table 3. Drug interactions

INTERACTION	DRUG
Pharmacokinetic	
• Increase in digoxin concentration	• Alprazolam • Amiodarone • Antibiotics (macrolides, tetracycline) • Atorvastatin • Cyclosporine • Dronedarone • Fluoxetine • Fluvoxetine • Ginkgo • Itraconazole • Ketoconazole • NSAIDs, including COX-2 inhibitors • Paroxetine • Propafenone • Protease inhibitors • Quinidine • Sertraline • Siberian ginseng • Simvastatin • Spironolactone • St John's wort • Tamoxifen • Verapamil
• Decrease in digoxin concentration	• Antacids • Cholestyramine • Neomycin • Penicillamine • Phenytoin • Rifampin • Sulfasalazine • Thyroid hormones
Pharmacodynamic	
• Might lead to advanced or complete heart block	• β-blockers • Non-dihydropyridine calcium channel blockers • Dronedarone
• Might lead to arrhythmias related to electrolyte level abnormalities or changes in sympathetic or parasympathetic tone	• Sennosides • Succinylcholine • Sympathomimetics • Thiazide or loop diuretics • ACE inhibitors • Intravenous calcium

ACE—angiotensin-converting enzyme, COX-2—cyclooxygenase-2, NSAID—nonsteroidal anti-inflammatory drug.
Data from Winter et al,[15] Ritschel and Kearns,[16] Ehle et al,[17] Hack,[18] Juurlink et al,[22] Gomes et al,[23] Guven et al,[24] Mathis and Friedman,[25] Wang et al,[26] and Yang et al.[27]

Conclusion

Digoxin toxicity can be a life-threatening condition. Practitioners involved in monitoring digoxin use need to maintain a high level of suspicion for digoxin toxicity. This includes the ability to recognize toxicity regardless of whether digoxin concentrations fall within the therapeutic range. Digoxin dosing should be based on ideal body weight. Monitoring of blood concentrations should occur at initiation and during times of physiologic change or when adding, adjusting, or removing medications known to interact with digoxin. Digoxin blood concentrations should be measured following the first distribution phase—at least 6 hours after the daily dose.

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Competing interests
None declared

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